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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,453	12/09/2004	Ogari Pacheco	4705-0106PUS1	5587

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EXAMINER	
HUANG, GIGI GEORGIANA	
ART UNIT	**PAPER NUMBER**
1609	

NOTIFICATION DATE	DELIVERY MODE
06/14/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/517,453	PACHECO ET AL.	
	Examiner	Art Unit	
	GiGi Huang	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *22-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21 and 26-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/14/2005, 12/09/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Claims 1-36 are present for examination at this time.

Claim Objections

2. Claims 22-25 are objected to under 37 CFR 1.75(c) as being in improper form because of multiple dependent claims 18-21. See MPEP § 608.01(n). Accordingly, the claims 22-25 not been further treated on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Claims 26-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The methods of manufacture steps do not state a specific concentration, weight, or final product form as an endpoint. This makes the claims indefinite as to what is the invention and leaves the metes and bounds of the claim unclear. Thereby the claims are rejected.

5. Claims 26-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to adding an alcoholic co-solvent, a medium chain mono/diglycerides mixture, and antioxidant, an emulsion-stabilizing agent, and a polarity corrector in the "appropriate amounts for the composition". The phrase is indefinite as it is unclear what the amounts for each component would be for the invention, leaving the metes and bounds of the claim unclear. Thereby the claim is rejected.

6. Claims 26-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to adding the surfactant under continuous stirring and "keeping stirring until complete mixture". The phrase is indefinite as it is unclear what is "keeping stirring until complete mixture". The composition is currently under continuous stirring. It could be to mix until clear, until the surfactant is dissolved, until a particular color change, or until a specific concentration for example. This phrase leaves the metes and bounds of the claims unclear. Thereby the claims are rejected.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipari et al. (U.S. Pat. # 6,232,333) in view of Bailey et al. (U.S. Pat. # 6,008,228).

Lipari et al. teaches a composition of proteinase inhibitors, specifically ritonavir, that have increased bioavailability. The composition is comprised of a protease inhibitor (ritonavir), fatty acid, alcoholic solvents, surfactants, and antioxidants.

The preferred ranges for the proteinase inhibitor (ritonavir) are from about 1 to about 50% (Col.8, lines 64-68, Col.9, lines 1-17) fulfilling the claims.

The fatty acid would be utilized in the preferred range of about 20% to about 99%.

The alcoholic solvents used include ethanol, propylene glycol, benzyl alcohol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400/PEG400 (also an emulsion stabilizer), and mixtures thereof to a preferred range of *about* 0% to *about* 15%, thereby fulfilling the claims (Col. 8, lines 26-35, Col. 9, lines 27-30, 37-43).

The surfactants taught included polyoxyl 35 castor oil (Cremophor ® EL), polyethylene glycol 40 hydrogenated castor oil (Cremophor ® RH 40), Tween ® 20, 40, 60, and 80 (polysorbates/polyoxythylene (20) sorbitan mono fatty acid esters). The preferred range for the surfactants taught are from about 0% to about 40% (Col. 8, lines 35-63, Col. 9, lines 30-36). Thereby fulfilling the limitations of the claims.

The antioxidants taught include BHT (butylated hydroxytoluene) and ascorbic acid, which is also a polarity corrector, in a preferred range of about 0.01% to about 0.08% (Col. 8, lines 8-12), Col.11, lines 33-40).

Lipari et al. does not expressly teach the use of a mono/diglyceride mixture or the specific use and range of PEG 400.

Bailey et al. teaches the use of monoglycerides and specifically the preferred mixture of medium chain mono/diglycerides C_8-C_{10} for proteinase inhibitor compositions, including ritonavir. Bailey teaches that proteinase inhibitors, being hydrophobic and/or lipophilic have difficulty being absorbed, especially due to crystal forms (polymorphs).

Bailey teaches that certain classes of glycerides used as carriers for formulation assist in alleviating these inadequacies. In fact they achieve better absorption and enhanced bioavailability with good stability/shelf life over a long period of time. The preferred combination was a mixture of medium chain mono/diglycerides C_8-C_{10} that was commercially available under many names including CAMPUL MCM®. The glycerides are derived from medium chain C_8-C_{10} fatty acids. The desired range for the glycerides for compositions containing about 120mg to about 300mg of proteinase inhibitor was 40-80% by weight.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the fatty acid for a mixture of medium chain mono/diglycerides C_8-C_{10}, as suggested by Bailey, and produce the instant invention as glycerides are derived from fatty acids, have equivalent properties, and are routinely substituted dependent on the desired physical properties of the composition.

One of ordinary skill in the art would have been motivated to do this because increase bioavailability and shelf life/stability of a ritonavir composition is desirable since the drug is known to have difficulty with crystal forms, stability, and bioavailability.

Bailey also teaches the specific ranges for the use of PEG 400 of 0-30% by weight for compositions containing about 120mg to about 300mg of proteinase inhibitor.

PEG is commonly used in substitution for fats since it has greater physical stability, so storage is better, they do not become rancid, and the release of the drug is not due to the melting point. In conjunction, PEG's can be more reactive than fats so an increased amount of antioxidant/polarity corrector may be needed and Bailey suggests a range of 0.01% to 0.5% that one of skill in the art would utilize as needed if the amounts taught by Lipari needed modification.

PEG is known to be used to enhance the aqueous solubility of poorly soluble compounds, like ritonavir, and are commonly used as a water-miscible solvent for compositions for gelatin capsules. They are also used for adjusting the viscosity of compositions, suspending agent, and emulsion stabilizers (see sheets on Polyethylene Glycol from Handbook of Pharmaceutical Excipients).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize a larger percentage of PEG 400, as suggested by Bailey, and produce the instant invention. The composition taught by Lipari utilized fatty acids on the range of about 20% to about 99%, and with the substitution of the CAMPUL® for the fatty acid, increased amounts of PEG 400 would be utilized, as suggested by Bailey, to compensate and provide added solubility for the ritonavir as a solvent, emulsion stabilizer, and viscosity agent which would be adjusted by one of skill in the art to the desired consistency. It would also provide greater stability for storage and better bioavailability having consistent release not subject to melting points in conjunction to improved properties of the CAMPUL ®.

One of ordinary skill in the art would have been motivated to do this because ritonavir is known for difficult bioavailability and stability so any modification to improve stability, storage, and bioavailability would be desirable. This would reduce costs and improves profits.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 26-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipari in view of Bailey as applied to claims 1-21 above, and further in view of CUBoulder Organic Chemistry Undergraduate Courses, Lab Techniques.

Lipari teaches the preparation of a ritonavir composition by combining a fatty acid and pharmaceutically acceptable alcohols.

They are mixed at room temperature (about 33°C, heat applied as necessary to 28°C to 37°C). The antioxidants are added, mixed, and the protease inhibitor (ritonavir) is added and stirred until dissolved. Surfactant is then added, mixed, filtered, and then

the appropriate volume (e.g. ritonavir 200mg) of the mixture corresponding to the desired dose is formulated into capsules (Col 21, lines 10-30, Col. 22, lines 25-55, Example 7, Col. 23, lines 35-68, Col. 30, Example 35). Bailey teaches the use of mono/diglycerides and its substitution for fatty acids are discussed above. Note that reversal/modification of the order of known steps of manufacture that produces the same product is not patentable.

Lipari in view of Bailey does not expressly teach the use of vacuum distillation.

CUBoulder Organic Chemistry Undergraduate Courses, Lab Techniques teaches vacuum distillation.

Vacuum distillation/evaporation is a common and basic process for removing solvent, condensing, and purifying a compound (ritonavir). The practice is used industrially and laboratories commonly in the form of the rotary evaporator. Being a basic and know skill and process, the technique is taught in school lab chemistry courses.

It is especially valuable in distilling compounds that might undergo decomposition on heating at atmospheric pressure, as it is used with or without heat, and used to remove solvents from the mixture without damaging the product (see Wikipedia sheets specific to vacuum distillation and CUBoulder sheets specific to vacuum distillation and solvent removal).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize vacuum distillation to thermal degradation of the drug, as suggested by CUBoulder Organic Chemistry Undergraduate Courses, Lab

Techniques to produce the instant invention as ritonavir is known, by applicants own admission, to have thermal degradation at higher temperatures.

One of ordinary skill in the art would have been motivated to do this because it would be a more stable method for producing the ritonavir composition and the method produces less residue build up which is important in commercial applications where temperature transfer is produced with heat exchangers (see Wikipedia sheets specific to vacuum distillation and CUBoulder sheets specific to vacuum distillation and solvent removal).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (In re Opprecht 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); In re Bode 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

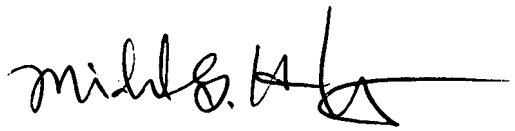
10. Claims 1-36 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GiGi Huang whose telephone number is (571) 272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH



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SUPERVISORY PATENT EXAMINER